

REMARKS**I. Status of the Application**

Claims 1-14 and 21-35 are pending in the application. Claims 15-20 have been withdrawn from further consideration as being drawn to a non-elected invention. Applicants have cancelled claims 3, 4, 15-20, 22 and 23 without prejudice to the filing of any appropriate continuation applications. Claims 1, 3-14 and 21-35 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 1, 3, 6-8, 10-12, 21, 22, 24-26, 28, 29 and 31-35 stand rejected under 35 U.S.C. §102(b) as being anticipated by Eitenmuller et al., U.S. Patent No. 4,610,692. Claims 4, 5, 9, 13, 14, 23 and 27 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Eitenmuller et al. in view of Pirhonen et al., U.S. Patent Pub. No. 2003/014029 A1, and Santos et al. (1998) *J. Biomed. Mater. Res.* 41:87. Claim 30 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Eitenmuller et al. in view of Pirhonen et al. and Santos et al., further in view of Hall, U.S. Patent No. 6,730,129. Applicants request entry and consideration of the foregoing remarks, which are intended to place this case in condition for allowance.

Applicants have amended the claims to more clearly define and distinctly characterize Applicants' novel invention. Specifically, claim 1 was amended to incorporate the subject matter of cancelled claim 4, and to address formal matters. Claim 21 was amended to incorporate the subject matter of cancelled claim 23, and to address formal matters. Claim 28 was amended to recite that the carrier is present on the surface of the scaffold, support for which can be found at least at paragraph 0030 of the specification, where Applicants teach the formation of carrier on the surface of scaffolds. Claims 5, 8, 13, 14, 26 and 31 were amended to

address formal matters. Applicants respectfully submit that the amendments presented herein do not raise new issues requiring further search, and add no new matter.

II. Claims 1, 3-14 and 21-35 Are Definite

At page 3 of the instant Office Action, claims 1, 3-14 and 21-35 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse these rejections.

The Examiner queries how the pyrrolidone is “arranged” with the scaffold in claims 1, 13, 14 and 21. Without acquiescing to the Examiner’s rejection, Applicants respectfully submit that claims 1, 13, 14 and 21 have been amended to remove the word “arranged,” thus rendering claims 1, 13, 14 and 21 definite. Accordingly, Applicants request that the rejections of claims 1, 13, 14 and 21 be reconsidered and withdrawn.

The Examiner questions what the term “one bioactive agent” is in claims 7 and 25. The second paragraph of 35 U.S.C. § 112 states that:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

It is well settled that a claim must “reasonably apprise those skilled in the art both of the utilization and scope of the invention.” *Georgia-Pacific Corp. v. United States Plywood Corp.*, 258 F.2d 124, 134-38, 118 U.S.P.Q. 122, 130 (2d Cir. 1958), *cert. denied*, 358 U.S. 884 (1958). Claims 7 and 25 meet this standard.

Applicants respectfully submit that the term “bioactive agent” is well known in the art and would be readily understood by one of skill in the art. The term “bioactive” is defined as “of

or relating to a substance that has an effect on living tissue: *bioactive compounds*” (Attachment A, The American Heritage Dictionary), and “having an effect upon a living organism, tissue, or cell. Biologically active. Antibiotic, enzymes, and vitamins are all bioactive substances” (Attachment B, MedicineNet.com). A bioactive “agent” is an agent having the bioactive properties described above. Applicants teach that bioactive agents may include anti-inflammatory agents, antibacterial agents, antiparasitic agents, antifungal agents, antiviral agents, anti-neoplastic agents, analgesic agents, anesthetics, vaccines, central nervous system agents, growth factors, hormones, antihistamines, osteoinductive agents, cardiovascular agents, anti-ulcer agents, bronchodilators, vasodilators, birth control agents, fertility enhancing agents and polypeptides, and bone morphogenic proteins such as OP-1, BMP-2, BMP-4, BMP-6 and BMP-7 (paragraph 0062).

Claims 7 and 25 are clear and definite because they reasonably convey to one skilled in the art what the invention is. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Examiner further queries how the carrier is “arranged” with the scaffold of claim 28. Without acquiescing to the Examiner’s rejection, Applicants submit that claim 28 has been amended to recite “wherein the carrier is present on a surface of the scaffold” thus rendering this claim definite. Accordingly, Applicants request that the rejection of claim 28 be reconsidered and withdrawn.

The Examiner asks how one distinguishes the carrier from the scaffold if both materials are ceramic, glass ceramic or glass material in claims 21 and 29. At the outset, Applicants respectfully submit that claim 21 does not recite a scaffold. Accordingly, Applicants request that the rejection of claim 21 be withdrawn.

Claim 29 and the claims from which it depends recite an implant comprising a scaffold on whose surface a carrier is arranged. Each of the carrier and the scaffold may be ceramic, glass ceramic or glass material. Applicants respectfully submit that one need not distinguish the carrier from the scaffold, and that claim 29 does not recite such a limitation. What the claim does recite is an implant comprising a scaffold on whose surface the carrier is arranged. Applicants respectfully submit that one of skill in the art would readily understand what is meant by “a scaffold on whose surface the carrier is arranged.” Applicants teach that a scaffold is a structure that serves as a base or substrate for the carrier. Applicants teach that such an implant may be made by immersing a scaffold in a simulated body fluid to form an Si-rich layer on the surface and calcium phosphate on the surface as a carrier layer (paragraph 0030). The carrier can then be used to adsorb one or more pyrrolidones (paragraph 0033). There is no reason to physically distinguish the carrier from the matrix and one of skill in the art would not need to do so in order to use the claimed implant. Accordingly, Applicants submit that claim 29 is definite and request that the rejection be reconsidered and withdrawn.

The Examiner queries what the “polymer material” of claim 31 is. Without acquiescing to the rejection, Applicants have amended claim 31 to remove the term “material” such that the claim recites that the “scaffold is made of a polymer.” Applicants respectfully submit that the term polymer is well known in the art, and that one of skill in the art would readily understand that which Applicant claims. Applicants teach polymers such as polysulphone, polyether-ether-ketone, polyether-ketone-ketone and poly(lactic-co-glycolic acid) (paragraphs 0049 and 0050).

III. Claims 1, 3, 6-8, 10-12, 21, 22, 24-26, 28, 29 and 31-35 Are Novel over Eitenmuller

At page 4 of the instant Office Action, claims 1, 3, 6-8, 10-12, 21, 22, 24-26, 28, 29 and 31-35 stand rejected under U.S.C. §102(b) as being anticipated by Eitenmuller et al., U.S. Patent No. 4,610,692. The Examiner is of the opinion that Eitenmuller et al. discloses a sintered tricalcium phosphate ceramic implant for filling bone cavities and for fixing bone fragments in a living body, comprising a discretely shaped, baked porous body of tricalcium phosphate, at least one therapeutically active ingredient impregnated into said porous body and distributed among the pores therein, and at least one coating of a biodegradable substance on at least a portion of said porous body impregnated with said therapeutically-active ingredient, wherein the therapeutically active ingredient is selected from the group including polyvinyl pyrrolidone iodine, and that the porous body can be impregnated with up to about 45% by weight of a therapeutically active ingredient. Applicants respectfully traverse this rejection. Applicants respectfully submit that for a reference to anticipate a claim, the reference must teach each and every element of the claim.

Claim 1 and claims depending therefrom are directed to a bone grafting material comprising a porous carrier of ceramic or glass ceramic or glass and at least one pyrrolidone, wherein the *pyrrolidone* is selected from the group consisting of *1-methyl-2-pyrrolidone* (NMP), *1-ethyl-2-pyrrolidone* (NEP), *2-pyrrolidone* (PB) and *1-cyclohexyl-2-pyrrolidone* (CP). Claim 21 and claims depending therefrom are directed to an implant comprising a carrier of porous ceramic or glass ceramic or glass, and at least one pyrrolidone, wherein the *pyrrolidone* is selected from the group consisting of *1-methyl-2-pyrrolidone* (NMP), *1-ethyl-2-pyrrolidone* (NEP), *2-pyrrolidone* (PB) and *1-cyclohexyl-2-pyrrolidone* (CP). Applicants have discovered that the claimed porous carrier including the claimed pyrrolidone(s) provides a grafting

material/implant that beneficially enhances and accelerates the formation of new bone or cartilage tissue (paragraph 0015).

Eitenmuller neither teaches nor suggests Applicants' porous carrier comprising NMP, NEP, PB and/or CP. Eitenmuller et al. is directed to a tricalcium phosphate implant optionally impregnated with the specific pyrrolidone polyvinyl pyrrolidone iodine (column 5, line 66 to column 6, line 6). Eitenmuller et al. fails to teach or suggest the use of any pyrrolidones other than polyvinyl pyrrolidone iodine, and fails to recognize the beneficial effects on bone and cartilage formation mediated by pyrrolidones in general, let alone the claimed pyrrolidones NMP, NEP, PB or CP. Instead, Eitenmuller et al. teaches that polyvinyl pyrrolidone iodine is used as a broad-spectrum microbicide and fails to recognize the use of any pyrrolidone for any uses other than microbicidal applications (column 8, lines 23-25; column 9, lines 1-7 and lines 58-62). Indeed, polyvinyl pyrrolidone iodine is an antiseptic agent (See Attachment C). The polyvinyl pyrrolidone associated with the iodine merely act as a carrier to make the handling of iodine easier as compared to water soluble solutions.

As Eitenmuller et al. fails to teach or suggest each and every element of the claimed invention, this reference fails to anticipate the claimed invention. Accordingly, Applicants request that the rejection of claims 1, 3, 6-8, 10-12, 21, 22, 24-26, 28, 29 and 31-35 under U.S.C. §102(b) as anticipated by Eitenmuller et al., U.S. Patent No. 4,610,692, be reconsidered and withdrawn.

IV. Claims 4, 5, 9, 13, 14, 23 and 27 Are Nonobvious Over the Cited Art

At page 5 of the instant Office Action, claims 4, 5, 9, 13, 14, 23 and 27 and 31-35 stand rejected under U.S.C. §103(a) as being anticipated by Eitenmuller et al., in view of Pirhonen et

al., U.S. Patent Pub. No. 2003/0104029 A1, and Santos et al. (1998) *J. Biomed. Mater. Res.* 41:87. The Examiner is of the opinion that it would have been obvious to the person having ordinary skill in the art to manufacture a composition comprising a porous carrier of glass material, N-methyl-2 pyrrolidone and a bone morphogenetic protein such as BMP-2, since both Pirhonen et al. and Santos et al. disclose the osteogenic properties of N-methyl-2-pyrrolidone and BMP-2, respectively. Applicants respectfully traverse this rejection.

For at least the reasons set forth above, Eitenmuller et al. fails to teach or suggest the claimed porous carrier comprising NMP, NEP, PB and/or CP. Further, Eitenmuller et al. fails to teach or suggest a bone grafting material/implant comprising a porous ceramic or glass ceramic or glass carrier including NMP, NEP, PB and/or CP and at least one bone morphogenetic protein (BMP). Indeed, the Examiner admits that Eitenmuller et al. does not explicitly disclose a composition comprising either 1-methyl-2-pyrrolidone and/or a bone morphogenetic protein. The secondary references fail to cure these deficiencies of Eitenmuller et al.

Applicants claim a bone grafting material/implant comprising a porous carrier of *ceramic* or *glass ceramic* or *glass* comprising at least one pyrrolidone, wherein the pyrrolidone is selected from the group consisting of NMP, NEP, PB and CP.

In contrast to Applicants' claimed invention, Pirhonen et al. is directed to resorbable *polymers* or *copolymers* such as films and membranes that are treated with NMP (paragraphs 0021, 0025, 0028). Pirhonen et al. teaches that their resorbable polymers can absorb NMP when immersed into it (paragraph 0039), and that *the polymer composition* has *osteogenic properties* (paragraph 0021). Pirhonen et al. does not test the effect of NMP on bone formation in the absence of polymer or in combination with any other materials. Accordingly, this reference provides no teaching that NMP in the absence of polymer would have a beneficial effect on bone

formation, or that NMP in combination with other substrates such as ceramic, glass ceramic or glass would provide any beneficial effect on bone formation. Accordingly, this reference fails to cure the deficiencies of Eitenmuller et al.

Santos et al. fails to cure the deficiencies of Eitenmuller et al. and Pirhonen et al. Santos et al. is concerned with the function of Si-Ca-P xerogels as a substrate for differentiation and development of osteoprogenitor cells (page 91, discussion). Santos et al. teaches the formation of a calcium phosphate layer on their xerogels, and that this layer can be used to adsorb BMP (page 90, right column, first full paragraph; page 91, right column, paragraph bridging page 91 and page 92). Santos et al. neither teaches nor suggests that *any* pyrrolidone, let alone NMP, NEP, PB and/or CP, included in their xerogels would have a positive effect on bone formation.

For at least these reasons, the combination of references cited by the Examiner fails to teach or suggest Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejection of claims 4, 5, 9, 13, 14, 23 and 27 and 31-35 under U.S.C. §103(a) as anticipated by Eitenmuller et al. in view of Pirhonen et al. and Santos et al. be reconsidered and withdrawn.

V. Claim 30 Is Nonobvious Over the Cited Art

At page 6 of the instant Office Action, claim 30 stands rejected under U.S.C. §103(a) as being anticipated by Eitenmuller et al., in view of Pirhonen et al. and Santos et al., further in view of Hall, U.S. Patent No. 6,730,129. The Examiner states that Hall discloses the use of a biocompatible material made of a metal, titanium, for implant in bone that is coated with a calcium phosphate substance and at least one bone growth stimulating substance. The Examiner is of the opinion that one would have been motivated to use a metal scaffold because the scaffold

provides a wider range and choice of implants to satisfy different applications to facilitate various bone growths, such as soft bones, and hard bones. The Examiner concludes that it would have been obvious to the person having ordinary skill in the art to manufacture an implant comprising a metal scaffold, with a porous carrier of calcium phosphate and N-methyl-2-pyrrolidone along with BMP-2 to increase osteogenic properties of the implant. Applicants respectfully traverse this rejection.

Claim 30 is directed to an implant comprising a carrier of porous *ceramic* or *glass ceramic* or *glass*, and at least one *pyrrolidone*; wherein the pyrrolidone is selected from the group consisting of *NMP*, *NEP*, *PB* and *CP*; wherein the implant comprises a scaffold, and wherein the carrier is present on a surface of the scaffold; and wherein the scaffold is made of metal.

Eitenmuller et al. in view of Pirhonen et al. and Santos et al. fails to teach or suggest the claimed invention for the reasons set forth above. Hall fails to cure the deficiencies of the primary references. The Hall reference is directed to a titanium implant having a coating comprising calcium phosphate and a growth-stimulating substance (TS) (column 1, lines 8-10; column 2, lines 60-64). Hall teaches that a growth-stimulating substance can be BMP (column 5, lines 28-34). Hall neither teaches nor suggests that *any* pyrrolidone, let alone NMP, NEP, PB and/or CP, included with their titanium implants would have a positive effect on bone formation.

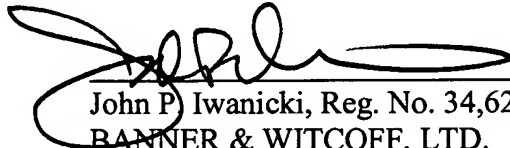
Thus, the combination of references cited by the Examiner fails to teach or suggest Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejection of claim 30 under U.S.C. §103(a) as anticipated by Eitenmuller et al., in view of Pirhonen et al. and Santos et al., further in view of Hall be reconsidered and withdrawn.

VI. CONCLUSION

Having addressed all outstanding issues, Applicant respectfully requests reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,

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over or along an edge for protection, reinforcement, or ornamentation. **5. Sports.** Fastenings on a ski for securing the boot. — **binding** *adj.* 1. Serving to bind. 2. Uncomfortably tight and confining. 3. Imposing or commanding adherence to a commitment, an obligation, or a duty: *binding arbitration*; *a binding agreement*. — **bind/ing-ly** *adv.* — **bind/ing-ness** *n.*

binding energy *n.* 1. The net energy required to decompose a molecule, an atom, or a nucleus into its components. 2. The net energy required to remove an atomic electron to an infinitely remote position from its orbit.

bin-dle-stiff (bīn'dl-stīf') *n.* A hobo, especially one who carries a bedroll. [English *bindle*, bundle (probably from German dialectal *bindel*, from Middle High German *bündel*, from *binden*, to bind, from Old High German *binten*; see **bhendh-** in Appendix) + **STIFF**.]

bind-weed (bīnd'wēd') *n.* 1. Any of various trailing or twining, often weedy plants of the genera *Calystegia* and *Convolvulus*, having white, pink, or purple bell-shaped or funnel-shaped flowers. 2. Any of various similar trailing or twining plants, such as the black bindweed.

bine (bīn) *n.* The flexible twining or climbing stem of certain plants, such as the hop, woodbine, or bindweed. [Alteration of **BIND**, vine.]

Bi-net-Si-mon scale (bī-nā'sē-mōn', -sī'mən) *n.* An evaluation of the relative mental development of children by a series of psychological tests of intellectual ability. Also called *Binet scale*, *Binet-Simon test*, *Binet test*. [After Alfred Binet (1857–1911) and Théodore Simon (1873–1961), French psychologists.]

Bing (bīng), Sir **Rudolf**. Born 1902. Austrian-born impresario who managed (1950–1972) the Metropolitan Opera in New York City.

Bing cherry *n.* A variety of cherry with juicy, sweet, deep red to nearly black fruit. [Perhaps after an employee of the cherry's originator.]

binge (bīnj) *n.* 1. A drunken spree or revel. 2. *a.* A period of unrestrained, immoderate self-indulgence. *b.* A period of excessive or uncontrolled indulgence in food or drink: *an eating binge*. — **binge** *intr.v.* **binged**, **bing-ing** or **binge-ing**, **bing-es**. 1. To be immoderately self-indulgent and unrestrained: "The story is like a fever dream that a disturbed and imaginative city-dweller might have after binging on comics" (Lloyd Rose). 2. To engage in excessive or uncontrolled indulgence in food or drink. [Dialectal *binge*, to soak.] — **bing'er** *n.*

SYNONYMS: *binge, fling, jag, orgy, spree.* The central meaning shared by these nouns is "a period of uncontrolled self-indulgence": *a gambling binge; had a fling between commencement and graduate school; a crying jag; an eating orgy; a shopping spree.*

binge-eat-ing syndrome (bīnj'ē'tīng) *n.* See **bulimia** (sense 2).

binge-purge syndrome (bīnj'pūj') *n.* See **bulimarexia**.

binge-vom-it syndrome (bīnj'vōm'it) *n.* See **bulimarexia**.

Bing-ham (bīng'am), **George Caleb**. 1811–1879. American painter noted for his portraits and genre paintings of the American frontier.

Bing-hām-ton (bīng'am-tən). A city of south-central New York near the Pennsylvania border south-southeast of Syracuse. It was settled in 1787. Population, 55,860.

bin-go (bīng'gō) *n., pl. -gos.* Games. A game of chance in which each player has one or more cards printed with differently numbered squares on which to place markers when the respective numbers are drawn and announced by a caller. The first player to mark a complete row of numbers is the winner. — **bingo** *interj.* Used to express the sudden occurrence of an event or completion of an action. [Origin unknown.]

bin-na-cle (bīn'ā-kəl) *n.* Nautical. A case that supports and protects a ship's compass, located near the helm. [Alteration of Middle English *bitakille*, from Old Spanish *bitacula* or from Old Portuguese *bitacola*, both from Latin *habitaculum*, habitation, from *habitare*, to inhabit. See **ghabh-** in Appendix.]

bin-oc-u-lar (bā-nōk'yā-lər, bī-) *adj.* 1. Relating to, used by, or involving both eyes at the same time: *binocular vision*. 2. Having two eyes arranged to produce stereoscopic vision. — **binocular** *n.* An optical device, such as a pair of field glasses or opera glasses, designed for simultaneous use by both eyes and consisting of two small telescopes joined with a single focusing device. Often used in the plural. — **bin-oc'u-lar/i-ty** (-lār'i-tē) *n.* — **bin-oc'u-lar-ly** *adv.*

bi-no-mi-al (bī-nō'mē-əl) *adj.* Consisting of or relating to two names or terms. — **binomial** *n.* 1. Mathematics. A polynomial with two terms. 2. Biology. A taxonomic name in binomial nomenclature. [From New Latin *binōmius*, having two names: *bi-* + French *nom*, name (from Latin *nomen*; see **NOMINAL).] — **bi-no/mi-al-ly** *adv.***

binomial distribution *n.* The frequency distribution of the probability of a specified number of successes in an arbitrary number of repeated independent Bernoulli trials. Also called *Bernoulli distribution*.

binomial nomenclature *n.* The scientific naming of species whereby each species receives a Latin or Latinized name of two parts, the first indicating the genus and the second being the spe-

cific epithet. For example, *Juglans regia* is the English walnut. *Juglans nigra*, the black walnut.

binomial theorem *n.* Mathematics. A theorem that specifies the expansion of a binomial to any power without requiring the explicit multiplication of the binomial terms.

bint (bīnt) *n.* Chiefly British & Offensive. A woman or girl: "As the R.A.F. friend would have put it, you could never tell with these foreign bints" (Kingsley Amis). [Arabic, daughter.]

bin-tu-rong (bīn-tōor'ōng, -ōng) *n.* A civet (*Arctictis binturong*) of southeast Asia with a long, prehensile tail. Also called *bearcat*. [Malay *binturong*, *binturong*.]

bi-nu-cle-ar (bī-nōō'klē-ər, -nyōō'-) *adj.* Variant of **binucleate**.

binuclear family *n.* The extended family, usually consisting of two separate households, formed by the children and subsequent spouses of the partners in a divorce.

bi-nu-cle-ate (bī-nōō'klē-īt, -āt', -nyōō'-) also **bi-nu-cle-ated** (-ā'tīd) or **bi-nu-cle-ar** (-klē-ər, -nyōō'-) *adj.* Having two nuclei.

Bin-ue (bīn'wā). See **Benue**.

bi-o (bī'ō) *n., pl. -os.* Informal. 1. A biography. 2. A biographical sketch or outline. — **attributive**. Often used to modify another noun: *bio cards*; *bio information*.

bio- or **bi-** *pref.* 1. Life; living organism: *biome*. 2. Biology; biological: *biophysics*. [Greek, from *bios*, life. See **gwei-** in Appendix.]

bio-ac-cu-mu-la-tion (bī'ō-ā-kyōōm'yā-lā'shən) *n.* The accumulation of a substance, such as a toxic chemical, in various tissues of a living organism: *the bioaccumulation of mercury in fish*. — **bi'ō-ac-cu-mu-la-tive** *adj.*

bi-o-a-cous-tics (bī'ō-ā-kōō'stīks) *n.* (used with *a sing. verb*). The study of sounds produced by or affecting living organisms, especially those sounds involved in communication.

bi-o-ac-tive (bī'ō-āk'tiv) *adj.* Of or relating to a substance that has an effect on living tissue: *bioactive compounds*.

bi-o-ac-tiv-i-ty (bī'ō-āk-tiv'i-tē) *n.* The effect of a given agent, such as a vaccine, on a living organism or living tissue.

bi-o-as-say (bī'ō-ās'ā, -ā-sā') *n.* Determination of the strength or biological activity of a substance, such as a drug or hormone, by comparing its effects with those of a standard preparation on a test organism.

bi-o-as-tro-nau-tics (bī'ō-ās'trō-nō'tīks) *n.* (used with *a sing. verb*). The study of the biological and medical effects of space flight on living organisms. — **bi'ō-as-tro-nau-ti-cal** *adj.*

bi-o-a-vail-a-bil-i-ty (bī'ō-ā-vā'lā-bil'i-tē) *n.* The degree to which a drug or other substance becomes available at the physiological site of activity after administration.

bi-o-bib-li-og-ra-phy or **bi-o-bib-li-og-ra-phy** (bī'ō-bīb'lē-ōg'rā-fē) *n., pl. -phies*. A book or article combining an account of a person's life with a discussion of works written by or about that person.

Bi-o-Bi-o (bē'ō-bē'ō). A river of central Chile flowing about 386 km (240 mi) generally northwest from the Andes to the Pacific Ocean near Concepción.

bi-o-cat-a-lyst (bī'ō-kāt'l-īst) *n.* A substance, especially an enzyme, that initiates or modifies the rate of a chemical reaction in a living body; a biochemical catalyst. — **bi'ō-cat-a-lyt/ic** (-kāt'l-īt'ik) *adj.*

bi-o-ce-nol-o-gy (bī'ō-sə-nōl'ə-jē) *n.* Ecology. The study of communities in nature and of interactions among their members.

bi-o-ce-no-sis also **bi-o-coe-no-sis** (bī'ō-sī-nō'sis) or **bi-o-ce-nose** (-sē'nōs) *n., pl. -ses* (-sēz). A group of interacting organisms that live in a particular habitat and form an ecological community.

biochemical oxygen demand *n.* Abbr. **B.O.D.** Microbiology. The amount of oxygen required by aerobic microorganisms to decompose the organic matter in a sample of water, such as that polluted by sewage. It is used as a measure of the degree of water pollution. Also called *biological oxygen demand*.

bi-o-chem-is-try (bī'ō-kēm'i-stre) *n.* 1. The study of the chemical substances and vital processes occurring in living organisms; biological chemistry; physiological chemistry. 2. The chemical composition of a particular living system or biological substance: *viral biochemistry*. — **bi'ō-chem/i-cal** (-i-kal) *adj.* & *n.* — **bi'ō-chem/i-cal-ly** *adv.* — **bi'ō-chem/ist** *n.*

bi-o-chip (bī'ō-chīp') *n.* Computer Science. A computer chip made from organic molecules rather than silicon or germanium.

bi-o-cide (bī'ō-sīd') *n.* A chemical agent, such as a pesticide that is capable of destroying living organisms. — **bi'ō-cid/ic** (-sīd'ik) *adj.*

bi-o-cli-ma-tol-o-gy (bī'ō-klī'mā-tōl'ə-jē) *n.* The study of the effects of climatic conditions on living organisms. — **bi'ō-cli-mat/ic** (-klī-māt'ik) *adj.*

bi-o-coe-no-sis (bī'ō-sī-nō'sis) *n.* Variant of **biocenosis**.

bi-o-com-pat-i-bil-i-ty (bī'ō-kəm-pāt'ā-bil'i-tē) *n.* The property of being biologically compatible by not producing a toxic, injurious, or immunological response in living tissue: *As a result of its strength and biocompatibility, the material is often used in medical devices*. — **bi'ō-com-pat/i-ble** *adj.*

bi-o-con-ver-sion (bī'ō-kən-vūr'zhən, -shən) *n.* The conversion of organic materials, such as plant or animal waste, into



binocular

THE
AMERICAN
HERITAGE
DICTIONARY

OF THE
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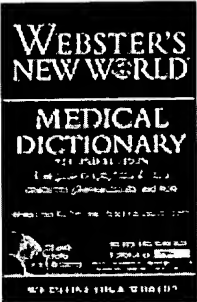
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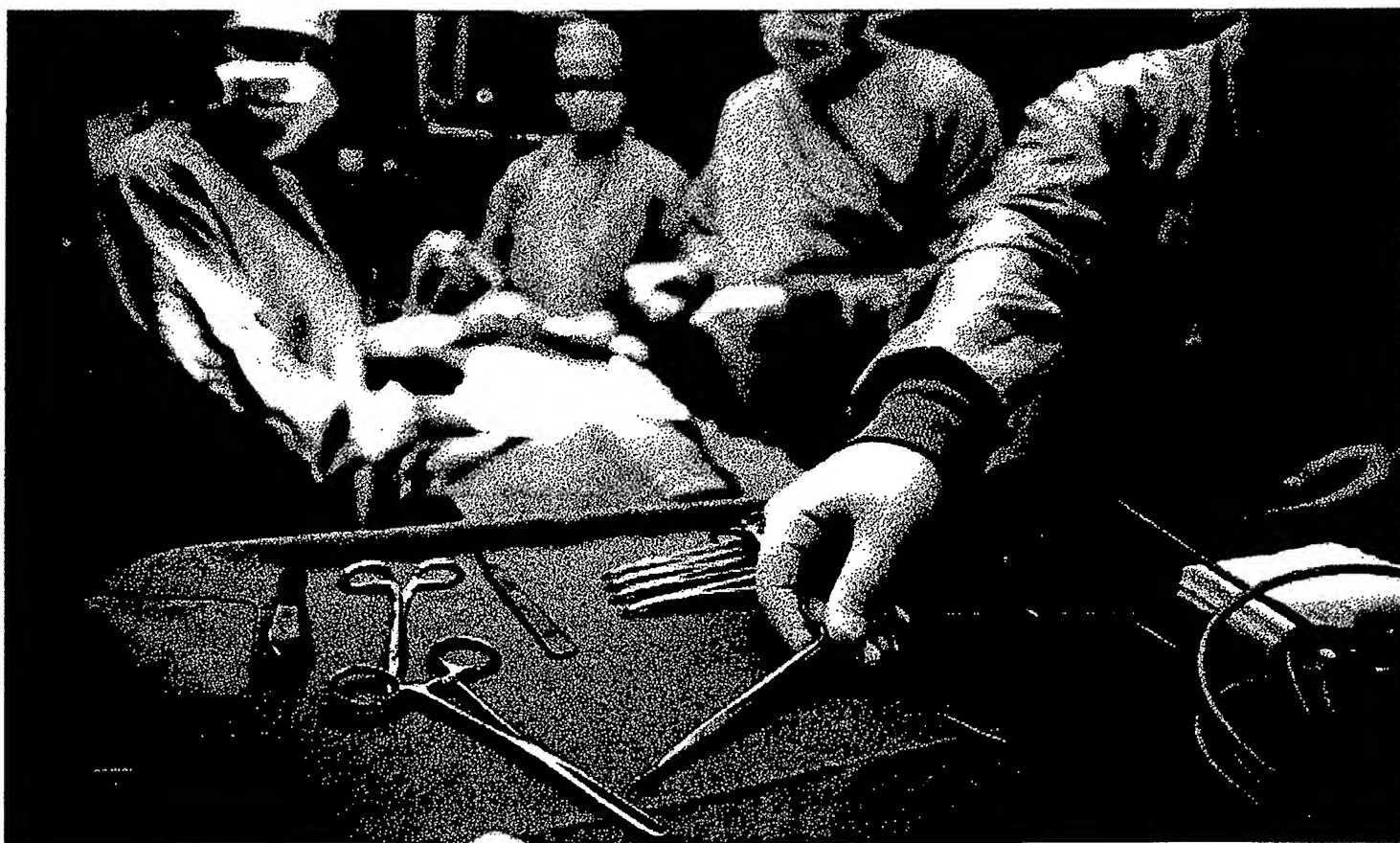
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PVP-IODINE

Povidone Iodine Antiseptic Agent



INTERNATIONAL SPECIALTY PRODUCTS

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INTRODUCTION

Iodine was discovered in 1812 by the French scientist Courtois who isolated this non-metallic essential element while treating seaweed ash with sulphuric acid to recover sodium and potassium compounds. Iodine was named for its deep-violet vapor by Guy-Lussac in 1814 after the Greek word "*ioeldes*" meaning violet colored.

While interesting, the new element had several properties which made its application unsatisfactory. Its inherent insolubility in water was overcome by dissolving the iodine in alcohol, but the alcoholic iodine solution itself exhibited serious drawbacks. First, the concentration of the solution constantly varied due to evaporation of the solvent. Furthermore, at concentrations higher than 5% the solutions were found to be irritating to the eyes, skin and mucous membranes. These problems were alleviated to a degree by adding some iodide to the iodine solution to yield the water soluble triiodide, but the irritating effect could not be completely eliminated through this formulation.

Despite these drawbacks, the value of a new disinfectant made from iodine was soon recognized and the water-alcohol solutions were quickly put in use. Lugol's Solution (aqueous solution containing 5% elemental iodine and 10% potassium iodide) was first made in 1829, and "*tincture of iodine*" was listed in the U.S. Pharmacopoeia by 1830.

Over the last century, scientists have developed a number of iodine compounds and preparations to overcome the adverse side effects of iodine, its painfulness on open wounds and the possibility of allergic reactions. The objective was to avoid such incompatibilities without a significant loss of germicidal efficacy. As a result, iodophors, such as PVP-iodine from ISP, were developed and have succeeded as ideal forms of application.

GENERAL PROPERTIES AND ADVANTAGES

PVP-iodine (Povidone-iodine), was introduced to the pharmaceutical market as an antiseptic agent in the 1950's and is as effective as iodine itself against a broad spectrum of disease-causing microorganisms.^{1,2} It differs from iodine, in that it is less irritating to the skin and does not require iodides or alcohol to dissolve. Additionally, PVP-iodine stains are water-washable. Early promotional materials refer to PVP-iodine as "*tamed iodine*" because of its safety. Furthermore, the poison label required for iodine products is not necessary in commercial preparations containing PVP-iodine.

PVP-iodine is used in both human and veterinary medicine to kill on contact a wide variety of bacteria, viruses, fungi, protozoa and yeasts. It has also been shown to be effective in controlling some insects. There has been no reported microbial resistance to PVP-iodine. At the same time, PVP-iodine is safer and easier to use than classic iodine preparations and has low systemic toxicity. Unlike iodine solutions, it is non-sensitizing and does not cause pain when applied to wounds or mucous membranes. PVP-iodine forms films that protect open wounds. These films can be washed in water and will not permanently stain skin, natural fibers or hard surfaces. PVP-iodine is exceptionally easy to use because it is soluble in water as well as in organic solvents, such as alcohols. As a result, it can be formulated in powders, tablets, lozenges, solutions, lotions, gels, ointments, creams, mousses or sprays.

The prolonged, non-selective, anti-microbial action of PVP-iodine is unparalleled for surface microbiocidal activity and is particularly effective in treating mixed infections. Its effectiveness has been clinically proven for all types of topical applications in both human and veterinary medicine.

INTRODUCTION

TYPICAL APPLICATIONS

- Skin antiseptics
- Surgical hand disinfection (scrubs)
- Wound cleansing
- Minor injury applications
- Treatment of burns
- Treatment of ulcers
- Applications in gynecology
- Dental and oral use
- Veterinary
- Aquaculture

SUMMARY OF PVP-IODINE PROPERTIES AND USES

PROPERTIES	USES
Broad spectrum biocide	Non-selective germicidal action Bactericide, fungicide, viricide, sporicide, amebicide, insecticide, nematocide Lacks the tendency for resistant micro-organisms to develop Effective in dilute solution Unparalleled for surface sterilization and in mixed infections
Detoxified iodine	Low animal and phytotoxicity Non-irritating to skin and mucous membranes Non-sensitizing Does not delay healing or formation of granulation tissue Non-stinging Reduced hazard if accidentally ingested
No detectable vapor pressure	Stable Can be bandaged without danger of burns (but occlusive conditions must be avoided) Retained where applied
Water-soluble	Ease of formulation Uniform concentrations Does not permanently stain
Film-forming	Prolonged germicidal action Adheres to treated surfaces where applied Color delineates treated area
Stable complex	No general odor No loss of iodine Rapid action even in presence of organic matter such as blood, pus, oil, grease, soap, etc.

PHYSICAL AND CHEMICAL PROPERTIES

PVP-Iodine is a stable chemical complex of polyvinylpyrrolidone (PVP) and elemental iodine.¹⁴

ISP supplies both pharmaceutical and technical grades of PVP-Iodine to support multiple applications. Table 1 lists some of the key specifications for each product.

Table 1: Key ISP Product Specifications

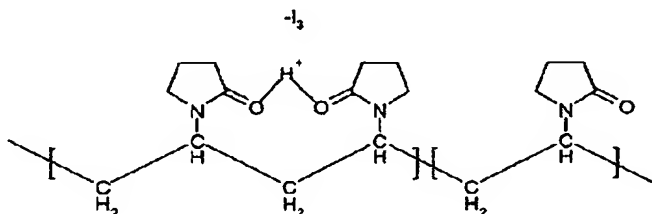
SPECIFICATIONS	PVP-iodine	iodone™ 10
Grade	Pharmaceutical	Technical
Pharmacopela Compliance	USP, Ph. Eur., JP	N/A
Appearance	Free flowing, reddish-brown powder	Free flowing, reddish-brown powder
Available Iodine	11.0 - 12.0%	10.0% Minimum
Iodine	6.0% Maximum	N/A
Loss on Drying	5.0% or 8.0% Maximum*	8.0% Maximum
Ash	0.025% Maximum	N/A
Heavy Metals	20 ppm Maximum	N/A

*Depending on grade.

DESCRIPTION

Chemical Description: Polyvinylpyrrolidone-iodine complex
 CAS Registry Name: 2-Pyrrolidone, 1-ethenyl-, homopolymer compound with iodine
 CAS Registry Number: 25655-41-8

CHEMICAL STRUCTURE



PHYSICAL AND CHEMICAL PROPERTIES

SOLUBILITY

PVP-Iodine (Povidone-iodine) is completely soluble in cold water in amounts up to and exceeding 10% (1% available iodine). By contrast, elemental iodine is water-soluble only to 0.034% at 25°C.

PVP-Iodine is also soluble in:

- ethyl alcohol
- isopropyl alcohol
- glycols
- glycerin
- acetone
- polyethylene glycol

VISCOSITY

As would be anticipated, the viscosity of PVP-Iodine solutions is a function of both the molecular weight of the polymer and the concentration of the solution. Typical data determined at 25°C for polymer complexes prepared from PVP K-30 is shown in Table 2.

Table 2: Viscosity of PVP-Iodine in Aqueous or Ethanolic Solutions

Solution Concentration %	Viscosity	
	Water mPa.sec	Ethanol mPa.sec
5	2.0	2.0
10	7.0	5.0
15	23.0	20.0

STABILITY

PVP-Iodine can be stored in powdered form without significant iodine loss. Samples kept for three years at 65°C in glass stoppered bottles without tape or seal showed only 0.5% maximum loss of available iodine. The product should, however, be protected from light and moisture.

Published data show the stability of PVP-Iodine solutions is vastly superior to that of iodine tincture or Lugol's solution.

COMPATIBILITY

PVP-Iodine dosage forms have been formulated successfully as powders, non-oral tablets, liquids, lotions, ointments, gels, mousses and sprays.

If the vehicle or base reacts with iodine, then the available iodine in the final preparation must be determined and adjusted, as necessary, since the germicidal activity of the finished product is dependent only on the level of non-complexed, free iodine. The amount of free iodine results from the iodine/iodide ratio and the molecular weight of the PVP used in the PVP-Iodine complex.

pH

The effective pH-range of PVP-Iodine is between 2.5 to 7 with an optimum between pH 3 to 6. Reducing agents and amino groups react with iodine lowering the amount of available iodine and increasing the amount of iodide. Shift of the iodine/iodide ratio to lower values and reduction in the amount of non-complexed free iodine results in reduced germicidal activity.

Compatibility of PVP-Iodine with other materials should be confirmed to avoid corrosion or incompatibility prior to use on hard surfaces or for disinfection of materials.

PARTICLE SIZE

Average particle size ranges from 90 to 140µ.
(Measured by Malvern Mastersizer 2003)

MODE OF ACTION

GERMICIDAL ACTION

The disinfecting characteristics of iodine arise from its ability to substitute for covalently bound hydrogens in compounds containing -OH, -NH, -SH, or CH functional groups. These groups can not only be part of the solvent or other constituents of the formula, but also of the material to be disinfected such as skin, mucous membranes, bacteria, etc.⁶

The exact solution-phase chemistry which yields the germicidal action is not easy to determine owing to the number of reactions which iodine may undergo in solution.

The chemistry of iodine in water can be described by a large number of reactions with eight of these being considered important. These reactions and their respective equilibrium constants are shown in Table 3.

These equations show that in aqueous solution iodine can exist in as many as seven different forms. It is also evident that since H^+ participates in many of the reactions, effects of solution pH are always important to the reaction pathways.

It has been shown that of the seven different forms of the iodine described in the reactions above only hydrated molecular iodine (I_2), hypiodous acid (HOI) and iodide ion (I^-) influence the antibacterial effect.^{7a}

In pharmaceutical formulations that contain both iodine and iodide, the bactericidal effect can almost entirely be attributed to free molecular iodine.⁷

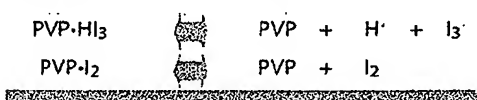
Table 3: Iodine-containing species in aqueous iodine solutions: Reactions and equilibria⁷

I_2				I^-	+	I		$K = 9.9 \times 10^9$
I_2	+	H_2O		H_2OI^+	+	I		$K = 1.2 \times 10^{11}$
I_2	+	H_2O		HOI	+	H^+	+	I^- $K = 3 \times 10^{-18}$
		HOI		I^-	+	OH^-		$K = 3 \times 10^{-16}$
		HOI		H^+	+	IO^-		$K = 4 \times 10^{-13}$
I_2	+	HOI		I_2HOI				$K = 2.7 \times 10^7$
I_2	+	I		I_3^-				$K = 7.14 \times 10^{-2}$
		$3HOI$		$3H^+$	+	$2I^-$	+	IO_3^- $K = 2.5 \times 10^{-11}$

MODE OF ACTION

In the presence of polymers having the ability to bind iodine (known as an iodophor property), the chemistry of iodine becomes even more complex. It is presumed that polymeric iodophors with oxygen-containing functional groups (e.g. carbonyl groups) will react with iodine to form donor-acceptor complexes in which the iodine is the acceptor.

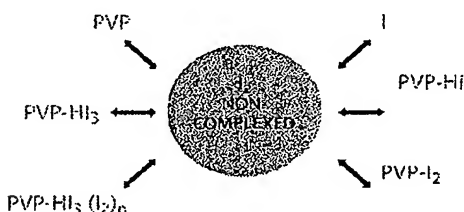
In PVP-iodine the iodophor consists of poly (*N*-vinyl-2-pyrrolidone) where at least two further reactions must be considered:



As is the case with all iodophors, the antibacterial activity of PVP-iodine is associated with the elemental iodine in the solution.

The difference between a conventional iodine solution and an iodophor is that the latter carries practically all the iodine in a complexed form, so that the concentration of the free iodine in the solution is always very low. This property has the effect of reducing the drawbacks associated with the presence of elemental iodine i.e. high toxicity, high level of irritation and staining power.

The bulk of the iodine exists in the triiodide form, which is in equilibrium with iodide and the active iodine.



In the PVP-iodine complex, the iodine does not exist as a single species and in fact several forms of iodine have been characterized:

- "Available iodine"
Contains all the iodine species which can be titrated with sodium thiosulfate
- "Iodide"
Negatively charged ion; necessary for the complexation of iodine
- "Total iodine"
Given by the sum of available iodine and iodide.
- "Free iodine"
The type of iodine which can be extracted from aqueous PVP-iodine solution.

BEHAVIOR OF THE PVP-IODINE COMPLEX

Elemental analyses, iodine determinations, and the results obtained using various physical methods have shown that PVP-iodine can be defined as a system in which for every two amide groups complexed with HI, there are an average of seventeen uncomplexed vinylpyrrolidone units in the molecule. Therefore approximately 80 mole % of the product is actually unaltered poly(vinylpyrrolidone) and hence should behave as such.

The determining factor for bactericidal activity is not the concentration of the "free iodine" in the solution but instead is the concentration of "free iodine" at the wall of the target bacterium. Polyvinylpyrrolidone itself has no bactericidal effect, but owing to its affinity for the cell membranes is able to deliver the active ingredient to the target.

It was also observed that the microbial action of such solutions increased on dilution, and a gradual decrease in activity only began when the dilution reached 1:100. This behavior seems to be independent of the duration of the interaction between PVP-iodine and the microorganisms.

MODE OF ACTION

In studies of PVP-iodine solution equilibria, the content of uncomplexed iodine initially increases with dilution reaching a maximum at a solution strength of 0.1% and then decreases upon further dilution (Figure 1). The other iodine species present in a PVP-iodine solution exhibit normal behavior in that their concentration decreases on dilution.

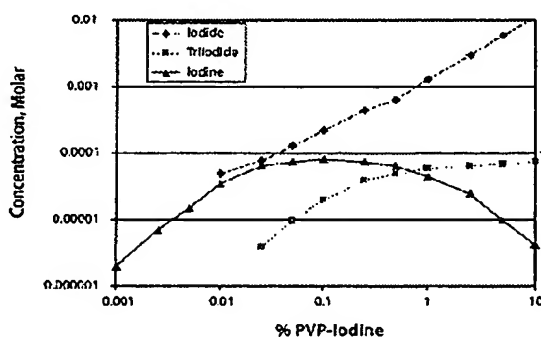


Figure 1: Equilibrium concentrations of PVP-iodine

Rackur explained this dilution phenomenon by the formation of polymeric aggregates which contain entrapped, uncomplexed iodine.⁹ Increasing the amount of solvent causes these aggregates to dissociate hence releasing the entrapped iodine and consequently increasing the antimicrobial efficacy of the solution.

By combining the results of the microbiological studies with the iodine equilibrium concentration curve (as shown in Figure 2) it becomes evident that the maximum iodine concentration and maximum microbial effect coincide. This provides strong confirmation that the concentration of uncomplexed iodine is the critical factor in PVP-iodine efficacy.

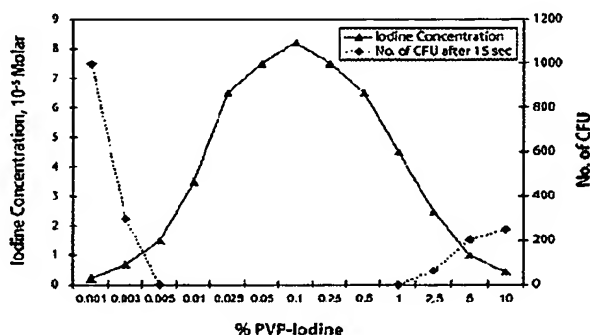


Figure 2: Correlation of the concentration of uncomplexed iodine with microbial reduction after 15 seconds for various concentrations PVP-iodine.⁷

(Mode of Action Section; Extracts taken from Analytical Profiles of Drug Substances and Excipients - Vol 25 1075-6280/98 Barabas & Brittain and references cited therein)

ANTIMICROBIAL ACTIVITY

IN VITRO BIOCIDAL ACTIVITY

For many years, iodine has been recognized as an effective broad spectrum biocidal agent.¹⁰ The irritancy and toxicity associated with its use have been significantly reduced by using PVP-Iodine.

The microbicidal action of PVP-Iodine, as discussed earlier, is related to the non-complexed, freely mobile elemental iodine, I_2 , the active form of which is polarized by water and hence can be considered to be H_2OI^+ in its final state. This activated iodine reacts in electrophilic reactions with enzymes of the respiratory chain as well as with amino acids from the cell membrane proteins both located in the cell wall. As a result, the well-balanced tertiary structure necessary for maintaining the respiratory chain is destroyed and the microorganism irreversibly damaged. Consequently, PVP-Iodine has a non-specific mode of action.

Biocidal agents have been classically measured for effectiveness by the use of *in vitro* methods. *In vitro* results, however, should be considered only as preliminary findings which should be confirmed under *in vivo* conditions simulating serum load and other organic matter in test samples. PVP-Iodine can react with these materials consuming some of the available iodine and thus reducing its germicidal efficacy.

The *in vitro* biocidal activity of PVP-Iodine has been studied for years against bacteria, yeast and molds, actinomycetes and rickettsia,¹¹ see Table 4.

SUMMARY

- PVP-Iodine kills microorganisms including bacteria, viruses, yeasts, molds, fungi and protozoa.
- Its microbicidal activity is that of a non-specific mode of action causing irreversible damage to the microorganism with no tendency to form resistance.
- Electrophilic reaction with enzymes of the respiratory chain located in the cell wall.
- Electrophilic reaction with amino-acids located in the cell wall.
- Damage of the necessary protein tertiary structure destroys the microorganism.

ANTIVIRAL ACTIVITY

There have been reports that PVP-Iodine is effective as an antiviral agent.

Eleven products containing PVP-Iodine were tested for their ability to inactivate human immunodeficiency virus (HIV) in a cell culture system.¹² All of the products completely inactivated the virus at PVP-Iodine concentrations greater than 0.5%, except for the lubricating antiseptic gel, which required 2.5%. Douche and medicated douche products did not inactivate HIV at the concentrations prescribed for usual clinical use (0.33% and 0.25%, respectively) but were effective at PVP-Iodine concentration of 0.5%.

Further studies have shown that PVP-Iodine 0.25% surgical scrub and solution inactivated HIV within seconds *in-vitro*, and if used in clinically achievable concentrations could serve as a surface disinfectant in hospital settings where HIV may be present.¹³

ANTIMICROBIAL ACTIVITY

Table 4: Microbiological Efficacy
Activity of PVP-Iodine versus Bacteria, Yeasts and Molds, Actinomycetes and Rickettsia ¹⁴⁷³

ORGANISMS (NO. of STRAINS)	RANGE OF PVP-I IN ppm AVAILABLE IODINE	CONTACT OF KILL TIME IN SECONDS
Proteus (41)	100 - 2500	15 - 180
Staphylococcus (36)	66 - 2500	15 - 80
Pseudomonas (36)	25 - 2500	15 - 900
Streptococcus (25)	200 - 2500	15 - 30
Escherichia (23)	200 - 2500	30 - 120
Salmonells (9)	1000 - 2500	15 - 60
Candida (8)	3.75 - 2500	10 - 120
Serratia (6)	200 - 2500	60 - 120
Spores-Bacillus; Clostridium (6)	10000	2 - 5 Hours
Trichomonas (5)	400 - 2500	30 - 60
Enterobacter (4)	1000 - 2500	60
Klebsiella (4)	500 - 2500	60
Clostridium (4)	1000	30 - 60
Shigella (3)	1000 - 2500	60
Corynebacterium (3)	2500	60
Diplococcus (3)	1000 - 2500	60
Mycobacterium (3)	1000 - 2500	60 - 120
Bacillus (3)	7.5 - 2500	10 - 30
Sarcina (2)	500 - 2500	60
Trichophyton (2)	1000	60
Aspergillus (2)	1000	30
Mima (1)	2500	60
Herella (1)	2500	60
Edwardsiella (1)	2500	60
Citrobacter (1)	2500	60
Providencia (1)	1000	60
Acinetobacter (1)	3.75	10
Epidermophyton (1)	1000	60
Microporum (1)	1000	60
Penicillium (1)	1000	30
Nocardia (1)	2500	60

ANTIMICROBIAL ACTIVITY

IN VITRO COMPARISON WITH OTHER ANTIMICROBIALS

BACTERICIDE

The antibacterial effect of PVP-Iodine, acetic acid and chlorhexidine gluconate was tested against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli*. PVP-Iodine was found to be the most effective.¹⁴

Furthermore PVP-Iodine solution and cream proved to be an effective antibacterial agent against methicillin-resistant (MRSA) as well as methicillin sensitive strains (MRSS) killing all within 30 seconds. This study also demonstrated that PVP-Iodine was more effective than chlorhexidine.¹⁵

Among the commonly used disinfectants including benzalkonium chloride, chlorhexidine gluconate and PVP-Iodine, the latter was found to yield the most rapid bactericidal effects against both MRSA and MSSA.¹⁶

Extensive studies were conducted in which 580 Gram-negative bacilli were investigated and 18.2% of the tested *Enterobacteriaceae* were found to be resistant to chlorhexidine digluconate, including 92.1% of those belonging to the *Proteus* strains. Four percent showed resistance to benzalkonium chloride (with 89.5% of the *Proteus* strains), but PVP-Iodine killed all the strains tested.¹⁷

The behavior of 29 bacterial strains, including *Pseudomonas aeruginosa*, *Serratia marcescens* and *Burkholderia cepacia* was studied against chlorhexidine gluconate, benzalkonium chloride, saponated cresol and PVP-Iodine. As many as 5 strains of *Pseudomonas aeruginosa* were found to be resistant to chlorhexidine gluconate and benzalkonium chloride, 3 strains of *Burkholderia cepacia* were resistant to chlorhexidine gluconate and 5 of the 8 strains of *Serratia marcescens* tested were resistant to chlorhexi-

dine gluconate and benzalkonium chloride. None of the strains were resistant to saponated cresol or to PVP-Iodine. The level of the bacteria tested was at the concentration recommended for disinfection of hands.¹⁸

ANTIVIRAL

Out of several disinfectants tested as antiseptics to inactivate HIV in the oral cavity, PVP-Iodine, benzalkonium chloride and chlorhexidine digluconate were found to be effective. PVP-Iodine, however, was the most effective of the three since it also yielded negative results in the HIV-specific plaque forming assay.¹⁹

Using Type I (Sabin strain) polio virus as the test organism, 5% PVP-Iodine was found to be rapidly virucidal.²⁰ In the same study, 2% glutaraldehyde was found to be similarly effective. However, 0.2% glutaraldehyde and noxythiolin were found to be less effective, while 0.05% chlorhexidine digluconate showed no virucidal activity.

ANTIMICROBIAL ACTIVITY

PVP-IODINE COMPARISON WITH CHLORHEXIDINE

PARAMETER	PVP-IODINE	CHLORHEXIDINE
Mode of Action	Activated iodine reacts by electrophilic reactions with enzymes of the respiratory chain as well as with amino acids from the cell membrane proteins both located in the bacterial cell wall. The tertiary structure necessary for maintaining the respiratory chain is destroyed and the micro-organism irreversibly damaged.	Adsorbs onto the bacterial surface causing a disorganization of the bilayered cytoplasmic membrane. The respiratory chain is interrupted, the membrane-bound ATPase is inhibited. At a certain concentration range, lysis of the cell wall resulting in release of the interior of the cell can occur. This can happen to red blood cells and explains why Chlorhexidine is limited to a single application for treatment of open wounds. PVP-Iodine does not have this limiting property.
Effective pH Range	Range	Range
	Optimum	Optimum
Microbiocidal Efficacy	Gram-positive	Gram-positive
	Gram-negative	Gram-negative
	Vegetative Bacteria	Vegetative Bacteria
	Bacterial Spores	Bacterial Spores
	Yeasts	Yeasts
	Fungi	Fungi
Use Concentration	Viruses	Viruses
	Bacteriophages	Bacteriophages
	10% to 0.01% PVP-Iodine (10% PVP-I, 1% available Iodine)	4% to 0.02%

* Fungistatic and fungicidal efficacy is subject to species variation.

* Infectivity of some lipophilic viruses e.g. influenza virus, adenovirus and herpes virus is inactivated.

ANTIMICROBIAL ACTIVITY

PVP-IODINE COMPARISON WITH CHLORHEXIDINE

PARAMETER	PVP-IODINE	CHLORHEXIDINE
Applications	Skin antiseptics	Y Skin antiseptics
	Surgical hand disinfection	Y Surgical hand disinfection
	Wound cleansing	Y Wound cleansing (single application only)
	Minor injury applications	Y Minor injury applications (single application only)
	Treatment of burns	Y Treatment of burns
	Treatment of ulcers	Y Treatment of ulcers
	Applications in gynecology	Y Applications in gynecology
	Dental and oral use	Y Dental and oral use
	Veterinary	Y Veterinary
Properties	Aquaculture	Y Aquaculture
	<ul style="list-style-type: none"> • Excellent water-solubility. • Non-irritating and low toxicity. • Polymeric iodophor complex acts as iodine reservoir which replaces used iodine. • Some persistence due to film-forming properties of Povidone. • Susceptibility to the presence of organic matter (reducing the germicidal capacity). 	<ul style="list-style-type: none"> • As base insoluble in water; some salts are readily soluble in water. • Inorganic ions precipitate chlorhexidine as insoluble salt. • Persistent action. • Toxic due to lysis of red blood cells. • Susceptibility to the presence of organic matter, less than PVP-Iodine. • Reversible staining of teeth surfaces when used as mouth rinse.

ANTIMICROBIAL ACTIVITY

IN VIVO STUDIES

Numerous *in vivo* studies made over approximately 35 years, as well as the widespread clinical use of products containing PVP-Iodine, indicate the efficacy of PVP-Iodine as a therapeutic agent for both humans and animals. Some of the publications supporting the clinical effectiveness of PVP-Iodine are reviewed below.

SKIN DISINFECTION

PVP-Iodine Surgical Scrub is a 7.5% PVP-Iodine solution (0.75% available Iodine) containing various agents for wound and skin cleansing. It should be rinsed off immediately after use to minimize skin irritation and healing retardation.

To reduce the presence of micro-organisms on skin and prevent infections a PVP-Iodine Topical Solution containing 10% PVP-Iodine (1% available Iodine) should be used. The PVP-Iodine film should remain on the skin so that it can act as a continued antimicrobial barrier.

To measure the efficacy of surgical scrubs, samples of scrub juices were taken to establish immediate, cumulative and persistent effects. The immediate effect is the reduction of bacteria found immediately after scrubbing.

A cumulative effect is seen when regular use of the scrub leads to increasing reductions of bacteria. The final measurement, persistence of effect, is defined as a decline in the post-wash bacterial count. Studies with PVP-Iodine scrubs show an effective, extensive immediate effect, a definite cumulative effect and a persistence of effect.²¹⁻²⁴

PRE-SURGICAL SKIN PREPARATION

Numerous studies indicate the efficacy of PVP-Iodine for pre-surgical skin preparation.²⁵⁻²⁸ There is also evidence that it is effective against spores present on the skin.²⁹

PVP-Iodine products have been widely used for pre-operative skin preparation and in various surgical procedures and shown to significantly lower subsequent infection rates.³⁰⁻³³

TREATMENT OF WOUNDS

PVP-Iodine Topical Solution (10% PVP-Iodine containing 1% available Iodine) is effective for ridding and preventing infections, including those with severe ulceration.³⁴⁻³⁷

PVP-Iodine has been shown to be an effective, fast acting and safe wound healing disinfectant.^{44,45} It can be used on mucous membranes without danger of burns, and is not only antiseptic but appears to augment wound healing.⁴⁶

TOPICAL APPLICATIONS

Topical PVP-Iodine Antiseptics, Aerosol Sprays, Ointments (5% PVP-Iodine, 0.5% available Iodine) and Creams (5% PVP-Iodine, 0.5% available Iodine) have been used to prevent microbial contamination in burns, incisions and infected ulcers.⁴⁷⁻⁵²

BURNS:

When used in the treatment of burns, PVP-Iodine effectively controls bacterial growth and protects the developing epithelium. Unlike many antibiotic agents it has the added advantage in that its continued use does not result in the generation of resistant organisms.⁵¹

ANTIMICROBIAL ACTIVITY

ULCERS:

PVP-Iodine, in solution or as an ointment, is particularly useful in the treatment of infected external skin ulcers where the maintenance of low bacterial count is of great importance.

PVP-Iodine containing preparations may be bandaged allowing exchange of humidity with the environment, but it is important to avoid occlusive conditions which could cause redness and skin irritation.

These products should not be used on deep wounds or serious burns without consulting a physician. Use should be discontinued if redness, irritation, swelling or pain persists or increases.

SCALP INFECTIONS:

Scalp and skin cleanser containing 7.5% PVP-Iodine has been reported to yield a significantly larger reduction of the microbial count in the scalp and hair versus products without PVP-Iodine.⁴⁴

MINOR SKIN ABRASIONS:

Cuts, bruises and lacerations which demand immediate attention in order to avoid serious infections are suitable for treatment with PVP-Iodine.

GYNECOLOGICAL APPLICATIONS

Douche and vaginal suppositories containing 10% PVP-Iodine have been reported effective in the treatment of vaginal infections.⁵¹⁻⁵² These can be used both as a topical and therapeutic

DENTAL AND ORAL USE

PVP-Iodine has been reported as a very effective bactericide against organisms commonly found in the mouth and is able to destroy these within 15 seconds.⁴³

Using a mouthwash/gargle product containing 0.5% PVP-Iodine is effective in reducing the bacterial flora in the mouth prior to dental surgery. It can also reduce the number of odor-causing bacteria.⁴⁴⁻⁴⁷

PVP-Iodine may cause less staining of the teeth versus chlorhexidine gluconate mouthwash.

PVP-Iodine has also been used to disinfect dental impressions made from silicon rubber and alginate.⁴⁸

VETERINARY MEDICINE

PVP-Iodine products have been used topically in the treatment of various swellings, chronic inflammatory conditions, sprains, bruises, obstinate ulcers and to disinfect the umbilical stump of foals and calves.

Due to its low toxicity and highly effective antimicrobial activity, topical PVP-Iodine applications have particular advantages in treating skin infections of cats, dogs or other animals that lick wounds.

PVP-Iodine has also been found to be highly effective in treating bacterial and fungal fish infections and minimizes infection of fish eggs, thereby increasing the breeding yield.⁷⁰⁻⁷¹

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